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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,246	12/16/2004	Mark Shipton	PG4857USw	8251

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,246	SHIPTON ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/16/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19-32 are rejected under 35 U.S.C. 102(b) as being anticipated by WO99/67262.

The compound appears in example 14, pages 122-123.

Claims 24-28 are composition claims, which would be embracive of aqueous solutions. Once the compound is dissolved, it loses its crystalline form and habit, and the exact same composition will be formed regardless of which form is employed. The reference has the same method of use as is set forth here.

Claims 19-23 are compound claims, and 29-32 are method claims, which require that the compound be administered in the particular habits set forth, and hence claims 29-32 not embrace aqueous solutions. This is alleged to be a form not present in the reference. However, no evidence for this is tendered. The reference is silent on the particular form. MPEP 2112 states:

"SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY

The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

In this case, the "unknown property" is the particular crystalline form. This is unknown because the reference is silent on this property. MPEP 2112 goes on to state:

"A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection."

Again, the "CHARACTERISTIC" which the prior art is silent on is the crystalline form.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. Here the reference explicitly teaches exactly what the compound is. The only difference is a characteristic about which the reference happens to be silent. See also Ex parte Anderson, 21 USPQ 2nd 1241 at 1251, discussion of Rejection E. There, the decision states, "There is ample precedent for shifting the burden to an applicant to reproduce a prior art product whose final structure or properties are, at least, in part determined by the precise process used in its manufacture." (page 1253). The "properties" branch of that statement applies here.

It is well settled that the PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical. An applicant's burden under these circumstances was described in *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) as follows:

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, or 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products (footnote omitted).

Overcoming the rejection is very straightforward. One simply replicates the prior art procedure. If the claimed form does not appear at all in the product, or if on repetition, it sometimes does not appear in the product, then the rejection is overcome.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 10481291. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is no line of demarcation.

As noted above, the composition claims when in form of aqueous compositions will be the same, so the aqueous solutions appear in both cases. With regard to claims 29-30, as set forth in the rejection below, it is not clear what the requirement of "spheronised habit" habit amount to. Moreover, the claims in 10481291 would cover the Form in any habit. Note there is ordinarily no patentable distinction between compositions of matter and methods. Hence, in the absence of a Terminal Disclaimer, an obviousness-type Double Patenting rejection may be made. See *In re Boylan,* 157 USPQ 370 [The patent had a composition of matter and a method of making it; the application had the method of use]; Ex parte MacAdams, 206 USPQ 445 [The patent had a composition of matter; the application had the method of use]; *Geneva Pharmaceuticals Inc. v. GlaxoSmithKline PLC,* 68 USPQ2d 1865 (CA FC 2003) [The earlier patent was drawn to method of use, the later three patents, held invalid in "Geneva II" were drawn to somewhat narrower versions of the composition of matter].

Claims 19-28, 31-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 10481291. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is no line of demarcation.

The same considerations pertain.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 19-32 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 10 of U.S. Patent No. 6677316. Although the conflicting claims are not identical, they are not patentably distinct from each other because of reasons given above. The reference is the equivalent to WO99/67262.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19, 22, 24, 27, 29, 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "spheronised habit" is indefinite. The examiner cannot locate any use of this term (or "spheronized habit") in the technical literature, and the term is not defined in the specification. There is no way of knowing where, exactly, the line is between something having a spheronized habit and one which does not. Likewise, there is no way of knowing

how to detect small amounts of spheronised habit material in larger quantities of non-spheronised habit material.

Claims 20-21, 23, 25-26, 28, 30 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There are two problems with the phrase "as polymorph I in a habit obtainable by a process of claim ..." This first is that it is not clear what "habit" means in this context. Ordinarily, the word refers to the type of geometric structure or shape that a given crystalline material forms. But these shapes don't have exact endpoints, so there is no clear way of saying whether two material with very similar but not identical shapes have the same habit, or different habits. Thus, if someone were to make the Polymorph I by a totally different method, and it were pretty similar to a product obtainable by a process of claim 16, how could one tell if it were the same habit, and this within claim 20, or just a close-but-different habit, and thus not in claim 20. The second problem is the "process of claim 17" is actual a broad collection of thousands of slightly different processes. For example, the toluene could be added in step a or in step b, and if in the second branch of step b, it could be added before or after seeding. It could be added in small, medium or large volumes. It could be chilled or not chilled. The seeding crystals could be large, medium or small (ground up). It could be spheronised (whatever that means) or not. There are different DMF to water ratios, and different solute concentrations, and the solution in step a could be anywhere up to the boiling point of the solvent mixture. The temperature could be lowered rapidly, slowly, or not at all (note that step b does not require cooling. If the initial solution was prepared at 20°C, the solution would just be allowed to stay at that temperature, or

even warmed up to 24°C). The claim 16 process has even more variables. There are many variations, and one would have to try them all to find out all the possible habits, to know what to compare to. One could never be sure that all the possibilities had been exhausted. Note that the claims are written in the "comprising" form, so additional steps, such as adding more water, or adding charcoal, scratching the vessel, etc. would have to be tried as well.

Claims 17-18, 21, 23, 26, 28, 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "the dilution is at least 15 volumes" is unclear. What is getting diluted by what? The compound is getting dissolved in a mixture of two solvents, so nothing is ever getting diluted.

Claims 29-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The first disorder is an unknown category. How would one determine that there isn't any advantage?

Claims 16-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "Polymorph II" and "Polymorph II" are not defined. Applicants need to insert into the claim some defining description of this material.

Claims 18, 23, 28, 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim says "adjusting the temperature to greater than 35°C." It thus reads on doing a crystallization purely by heating a solution, even to the boiling point. This cannot be deemed enabled. Crystallizing material purely by heating (i.e. with no addition of anti-solvent or seeding etc.) is not ordinarily achievable, owing to the fact that solubility rises with temperature. In the actual working example 2, the solution was cooled slightly, and anti-solvent was added and seeding was performed.

Claims 29-32 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.
The analysis is as follows:

(1) Breadth of claims.

A. As noted above, the first category is of unknown scope

B. CNS disorders covers a vast array of neurological disorders, essentially all such disorders except for peripheral neurological disorders. This includes neuritis, certain kinds of blindness and deafness as well as loss of sense of taste or smell, autism, meningitis, Vasovagal Syncope, synesthesia, Attention Deficit and Hyperactivity Disorder, Brown-Sequard Syndrome, many different types of convulsive disorders, apnea and other sleep disorders, Chronic relapsing polyneuropathies (such as idiopathic polyneuritis porphyria, and Beriberi) mental retardation, brain cancers and others cancers of the nervous system, an assortment of sensory integration disorders (such as Irlen syndrome), various types of facial pain (e.g. Trigeminal Neuralgia, Glossopharyngeal neuralgia, post herpetic neuralgia, and atypical facial pain) movement disorders (such as Tourette's syndrome or Restless Leg Syndrome) and other pains in the head (e.g. Tolosa Hunt Syndrome and cluster headaches), a wide range of anxieties, phobias, OCDs and psychotic disorders, depression, Delirium, and much more.

Some of these are categories which include contradictory problems. For example, sleep disorders covers insomnia and narcolepsy (which are opposites) as well as problems transitioning from one stage of sleep to another and apnea.

Some categories are extraordinarily diverse. Neurodegenerative disorders covers a broad array of different disorders that have different modes of action and different origins. The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; the vascular dementias (which are usually caused by cerebral infarction and include multi-infarct dementia (MID), strategic infarct dementia,

LID, ThD, and Binswanger's disease); Lewy Body dementia; Senile dementia of the neurofibrillary tangle type ("tangle-only dementia"); Gerstmann-Straussler-Scheinker Disease (GSS); Pick's disease, dementia of the frontal lobe type (DFT) and DFT with motor neuron disease (DFT-MND); Hallervordon-Spatz disease; progressive familiar myoclonic epilepsy; Corticodentatonigral degeneration; progressive supranuclear palsy (Steele-Richardson-Olszewski); Huntington's disease; more than a dozen dementias collectively called "frontotemporal dementia and Parkinsonism linked to chromosome 17" (FTDP-17); Tourette's syndrome; Shy-Drager syndrome; Senile dementia of the neurofibrillary tangle type ("tangle-only dementia"); Lafora disease, cortical-basal ganglionic degeneration (CBGD); Ramsay Hunt Syndrome Type II; Friedrich's ataxia and other spinocerebellar degenerations; Olivopontocerebellar atrophy (OPCA); spasmotic torticollis; Striatonigral degeneration; various types of torsion dystonia; certain spinal muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary lateral sclerosis; peroneal muscular atrophy (Charcot-Marie-Tooth); Creutzfeldt-Jakob Disease (CJD); Hypertrophic interstitial polyneuropathy (Dejerine-Sottas); ophthalmic disorders such as primary open-angle glaucoma (POAG) and retinitis pigmentosa; Leber's Disease; Alper's disease; Wallerian degeneration, and Hypertrophic interstitial polyneuropathy. These exhibit a very broad range of effects and origins. For example, some give no dementia and affect only vision, such as POAG. Some give progressive dementia without other prominent neurological signs, such as Alzheimer's Disease, whereas other dementias have such signs, such as Diffuse Lewy Body Disease. Some give seizures and myoclonus, e.g. Lafora disease and Alper's disease, but most do not. Lewy Body Dementia gives a combination of parkinsonian effects, fluctuating cognition

and visual hallucinations not seen in other neurodegenerative disorders. Some give muscular wasting without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-Hoffmann. Some cause deafness e.g. Alper's disease, which is believed to be a metabolic disorder. Some are abnormalities of posture, movement or speech, such as Striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some are linked to tau mutations, such as Alzheimer's Disease and FTDP-17, and other such as Parkinson's clearly do not. Lafora disease (which is a hereditary) is characterized by the presence of inclusion bodies, known as Lafora bodies, within the cells of neurons. Alper's disease causes status spongiosus of the cerebral grey matter. Some affect only vision such as retinitis pigmentosa, while others affect both vision and cognitive functions, such as Posterior cortical atrophy (PCA). Even within those that fall into the same category of effects, there are often striking differences. For example, Alzheimer's Disease and Pick's disease both give progressive dementia without other prominent neurological signs. But the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical filaments of Alzheimer's Disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's Disease. Some normally strike young children (e.g. Alper's disease also known as progressive infantile poliodystrophy), some in adolescence (e.g. Lafora disease), some are primarily seen in middle age (most forms of frontotemporal dementia strike in the 40s or 50s), others are seen almost entirely in the aged e.g. Binswanger's disease, and some have no age distribution at all (e.g. CJD).

There are a wide assortment of Demyelinating Diseases, in two broad categories. Primary demyelination is a loss of myelin sheaths with relative preservation of the

demyelinated axons, arising either from damage to the oligodendroglia from a direct attack on the myelin itself. Secondary demyelination, occurs following axonal degeneration. For example, Leukodystrophies are diseases of the white matter resulting from an error in the myelin metabolism, giving impaired myelin formation. Each involves the deficiency of a different enzyme. Examples include Krabbe's disease, Adrenoleukodystrophy (which exists in 4 forms), adrenomyeloneuropathy, Alexander Disease, Canavan Disease, Metachromatic Leukodystrophy (which exists in three forms), Pelizaeus-Merzbacher Disease, Refsum Disease, and Zellweger Syndrome. No pharmaceutical treatment is available to any of the leukodystrophies. Acute Necrotizing Hemorrhagic Leukoencephalitis is believed to be mediated by autoimmune attack on CNS myelin, triggered by a viral infection. It is usually fatal, generally just within days on onset. Other examples include Multiple Sclerosis (MS), progressive multifocal leukoencephalopathy, and Acute Disseminated Encephalomyelitis. Some are inherited diseases, such as peroneal muscular atrophy, hypertrophic polyneuropathy and Refsum's diseases.

Another category is the toxic neuropathies. These are quite diverse owing to the huge range of things that cause such neuropathies. Thus, in the category of sensory damage to axons, there are Almitrine, Chloramphenicol, Dioxin, Doxorubicin, Ethambutol, Ethionamide, Etoposide (VP-16), Gemcitabine, Glutethimide, Hydralazine, Ifosfamide, Interferon-a, Isoniazid, Metronidazole, Misonidazole, Nitrous oxide, Phenytoin, Propafenone, Pyridoxine, Statins, and Thalidomide. Causing motor damage to Axons are Almitrine, Chloramphenicol, Dioxin, Doxorubicin, Ethambutol, Ethionamide, Etoposide (VP-16), Gemcitabine, Glutethimide, Hydralazine, Ifosfamide, Interferon-a, Isoniazid, Metronidazole, Misonidazole, Nitrous oxide, Phenytoin, Propafenone, Pyridoxine, Statins,

Thalidomid. Causing both types of damage are Acrylamide, Ethanol, Allyl chloride, Arsenic, Cadmium, Carbon disulfide, Chlorphenoxy, Ciguatoxin, Colchicine, Cyanide, Dapsone, Disulfiram, DMAPN, Ethylene oxide, lead, Lithium, Methyl bromide, Nucleosides (ddC; ddI; d4T), Nitrofurantoin, Organophosphates, Platinum analogs (Carboplatin, Cisplatinum, Oxaliplatin), Podophyllin, PCBs, Saxitoxin, Spanish toxic oil, Taxol, Tetrodotoxin, Thallium, Trichloroethylene, TOCP, Vacor (PNU), and Vinca alkaloids. In addition, demyelinating can be caused by Buckthorn, Chloroquine, Diphtheria, FK506 (Tacrolimus), Hexachlorophene, Muzolimine, Perhexiline, Procainamide, Tellurium, and Zimeldine. And moreover, both damage to axons and demylination is seen with Amiodarone, Ethylene glycol, 1,1'-Ethylidinebis[tryptophan], Gold, "Hexacarbons" (n-Hexane, n-butyl ketone, 2,5-hexanedione), Na Cyanate and Suramin. There is also postvaccinal encephalitis where the toxin arises from the vaccination.

There are also metabolic neuropathies. One category is that of the Mitochondrial Encephalomyopathies, which arise from of disorders affecting mitochondrial metabolism, including substrate transport, substrate utilization, defects of the Krebs Cycle, defects of the respiratory chain, and defects of oxidation/phosphorylation coupling. These neuropathies can result in the weakness of e.g. the proximal facioscapulohumeral, orbicularis and extraocular muscles. Other metabolic neuropathies originate from e.g. diabetes. The metabolic disorder Mucopolysaccharidosis I is the cause of Hurler's syndrome which causes progressive mental retardation.

Also included are CNS cancers, which covers a very diverse range of cancers in many categories and subcategories. There are an immense range of neuroepithelial tumors. These include astrocytic tumors (e.g. astrocytomas and glioblastoma multiform)

oligodendroglial tumors, Ependymal cell tumors (e.g. myxopapillary ependymoma), mixed gliomas (e.g. mixed oligoastrocytoma and ependymo-astrocytomas) tumors of the choroid plexus, neuronal and mixed neuronal-glial tumors (e.g. gangliocytoma, gangliogliomas, central neurocytoma, dysembryoplastic neuroepithelial tumor, esthesioneuroblastoma), pineal parenchyma tumors (e.g. pineocytoma, pineoblastoma), embryonal tumors (e.g. medulloepithelioma, neuroblastoma, retinoblastoma, ependymoblastoma) and others such as polar spongioblastoma and Gliomatosis cerebri. A second Division is tumors of the meninges. This includes tumors of the meningothelial cells, including Meningiomas (including fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, clear cell, chordoid, lymphoplasmacyte-rich, and metaplastic subtypes) and others such as papillary anaplastic meningioma. The category also includes non-meningothelial tumors of the meninges. Examples are benign mesenchymal tumors (e.g. osteocartilaginous tumors), malignant mesenchymal tumors (e.g. chondrosarcoma, hemangiopericytoma, rhabdomyosarcoma and meningeal sarcomatosis) primary pelanocytic Lesions (e.g. diffuse melanosis, melanocytoma), hemopoietic neoplasms (e.g. plasmactoma). A third Division are the tumors of Cranial and Spinal Nerves. This includes schwannomas, neurofibroma, and malignant peripheral nerve sheath tumor (MPNST). A fourth division are Germ Cell Tumors, including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma. A fifth division are the tumors of the Sellar Region, viz. pituitary adenoma, pituitary carcinoma and craniopharyngioma. Yet another division are local extensions from regional tumors, including paraganglioma, chodroma, chordoma, and chondrosarcoma. And there are many, many others.

It also covers a broad assortment of what are essentially memory or impairment of understanding or skill disorders. These include acquired language disorders, such as aphasias (e.g. conduction aphasia), apraxia, dysarthria, alexia, receptive dysphasia, and agraphia. It includes many types disorders called amnesias. There is anterograde amnesia (new events are not transferred to long-term memory) and retrograde amnesia (inability to recall events that occurred before the onset of amnesia). There is lacunar amnesia (loss of memory about one specific event), Fugue amnesia (Psychogenic amnesia or hysterical amnesia, including "repressed memories"), Childhood amnesia (inability to remember events from early childhood), Transient Global Amnesia (total memory loss), those arising from complex partial seizures, and alcoholic blackouts. It also includes various agnosias, such as Prosopagnosia, Integrative agnosias, asogmatoagnosia, Associative agnosias, Time Agnosia, Apperceptive agnosia, object agnosia, finger agnosia, phonagnosia, central achromatopsia, topographical agnosia, dyslexia, dyscalculia, right-left disorientation, Optic ataxia and Ocular apraxia, Color Agnosia, Simultanagnosia, Anosognosia, Auditory Agnosia (including amusia and word meaning deafness), and Somatosensory Agnosia (including Microsomatagnosia, Macrosomatagnosia, tactile agnosias and astereoagnosia), constructional dyspraxia, and more general processing disorders such as Cerebral Visual Impairment (CVI).

C. Peripheral vascular disorders includes Raynaud's disease, acrocyanosis, frost bite, acute arterial occlusion, phlebitis, phlebothrombosis, diabetic gangrene, causalgia, shock and pheochromocytoma; intermittent claudication, digital ulceration, peripheral occlusive vascular disease, diabetic retinopathy and various lower extremity problems.

D. The claims covers several other diseases and categories as well

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is non-existent. The dosage range information is missing.

(4) State of the Prior Art: The compounds is an oxadiazole derivative of an adenine, which a particular substitution pattern at two positions. So far as the examiner is aware, no oxadiazole derivatives of an adenine of any kind have been used for the treatment of such disorders.

(5) Working Examples: There are none to treatment of any disorder, or indeed, and data at all.

(6) Skill of those in the art: The skill level varies extremely widely, because CNS disorders covers so many diverse disorders. Origins can be extremely diverse. CNS disorders can be mediated by any of the 17 known neurotransmitters, and some involve more than one; there are dozens of different receptors which may be involved. Some arise from slow acting viruses, such as Subacute sclerosing panencephalitis and Progressive multifocal leucoencephalopathy. Some come from prions, such as kuru and CJD. Some are inflammatory disorders, such as granulomatous vasculitis of central nervous system, and isolated vasculitis of central nervous system. Others arise from autoimmune disorders, e.g. Multiple sclerosis, Rasmussen's syndrome, and Hashimoto's Encephalitis. Still others arise from bacteria, liver failure, immunizations, and metabolic disorders. Still others such

as ADHD, mental retardation and autism have no established biochemical mechanism or clear case. CNS cancers are so diverse that notion of any agent (let alone a large genus of compounds) being effective generally is absurd. Further, one skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. Among the neurodegenerative disorders, there are great differences in origins, even with what little is known. Thus, among progressive dementias, CJD is definitely caused by an infectious agent; so far as can be determined, this is not so for Huntington's disease. Even among the hereditary disorders, the origins are clearly different. Thus, FTDP-17 comes from chromosome 17, Huntington's Disease from chromosome 4, and the neurodegenerative disorder that people with Down's syndrome develop later in life is presumably connected in some way to chromosome 21. Sensory processing disorders can have a wide diversity of sources. For example, CVI can arise from Infection (meningitis, encephalitis and infected intracranial aneurysms), genetic defects, hydrocephalus, serious head trauma and stroke.

The great diversity of diseases falling within the "neurodegenerative disorder" category means that it is contrary to medical understanding that any agent (let alone a genus of trillions of compounds) could be generally effective against such diseases. The

intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. The vast majority have no treatment at all and many of them are very difficult to even get a clear diagnosis on. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive research effort on Alzheimer's Disease has produced are almost entirely means of providing Acetylcholinesterase inhibition, unrelated to the mechanism of action in this case.

In fact, the great majority of CNS disorders have no pharmacological treatment at all, and of those that do, none or virtually none have been treated with such inhibitors as are disclosed here. In addition to many brain tumors, important and devastating diseases such as mental retardation and autism and ALS and dyslexia have no pharmaceutical treatments at all. Current drug therapies for Parkinson's disease are aimed at symptomatic relief, primarily through dopamine replacement therapy, but do not actually treat the disease itself.

Problems occur for other uses as well. Some Peripheral vascular disorders are untreatable, as is stroke, except for certain anti-clotting drugs, which property these compounds are not disclosed to have.

(7) The quantity of experimentation needed: Especially in view of factors (1), and (6), the quantity of experimentation involved is expected to be especially high. Neurodegenerative disorders and brain tumors, for example, are among the most difficult categories of disorders to research.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full

scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Specification and Drawings

Figure 3 refers to "MIBK". The specification does not define this term. Applicants must either correct the drawing to remove, or correct the specification. Applicants are cautioned against introducing new matter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Mark Berch/

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Art Unit 1624

1/19/06